INTEGRINS AS MECHANOCHEMICAL TRANSDUCERS. D.E. Ingber. Dept. of Pathology, Brigham and Women's Hospital & Harvard Medical School, and Dept. of Surgery, Children's Hospital, Boston, MA 02115.

How do cells sense physical forces and transduce mechanical information into a biochemical response? For the past ten years, we have been exploring the possibility that mechanical forces are transferred across the cell surface via transmission across transmembrane receptors, such as integrins, that mediate cell attachment to extracellular matrix (ECM). This concept emerged out of studies analyzing the biomechanical mechanism by which ECM molecules regulate cell form and function. Experiments with cultured cells (e.g., endothelial cells, hepatocytes, smooth muscle cells) reveal that the growth and differentiation-modulating effects of ECM molecules depend on their ability to resist cell-generated tractional forces and thereby support cell and nuclear spreading (In Vitro 23:387,1987; J. Cell Biol. 109:317,1989; P.N.A.S. 87:3579,1990). A separate series of studies demonstrated that binding of ECM molecules to cell surface integrin receptors acts directly to regulate cell sensitivity to soluble mitogens (e.g., FGF, EGF, PDGF) by activating chemical signaling pathways inside the cell (J. Cell Biol. 110:1803,1990; Exp. Cell Res. 195:533,1991; P.N.A.S. 88:7849,1991; J. Cell Biol. 115:130a & 245a,1991). Signaling pathways activated by integrin binding include the Na^+/H^+ antiporter, inositol lipid turnover, and tyrosine kinases (e.g., c-src). However, while activation of these pathways is necessary for growth, it is not sufficient; large-scale changes of cell shape are also required.

Thus, additional studies have been carried out to determine whether cells also use a "mechanical signaling system" in order to regulate their growth and function. This hypothesis is based on studies with three dimensional "tensegrity" (tensional integrity) structures that are constructed by interconnecting multiple compression-resistant struts with a continuous series of tension elements that can vary in length in response to force (Chest 99:34s, 1991). These modelling studies revealed that cell, cytoskeletal, and nuclear form alterations could result from the action of tensile forces generated within the cytoskeleton and resisted by ECM attachment points. Recently, we asked whether cells utilize a structural system that depends on tensional integrity by carrying out experiments with permeabilized endothelial cells (J. Cell Biol. 115:394a,1991). These experiments confirmed that the structural stability of the cell and nucleus depends on a dynamic balance of tensile and compressive forces. Mechanical tension is generated within contractile microfilaments via an actomyosin filament sliding mechanism similar to that found in muscle, transmitted across transmembrane integrin receptors, and resisted by ECM anchoring points. When cytoskeletal tension overcomes the mechanical resistance of the substratum in a spread cell, rapid and coordinated retraction of the cell, cytoskeleton, and nucleus result.

These studies suggest that activation of a cellular response does not result from introduction of mechanical loads where there were previously none. Rather, all mechanical loads are imposed on a pre-existing cellular force balance. As transmembrane receptors which physically interlink ECM with elements of the structural cytoskeleton, integrins are excellent candidates as cellular force sensors or receptors (Curr. Opin. Cell Biol. 3:841,1991). If cells utilize an architectural system which depends on tensional integrity then forces that are transmitted across integrins may be tranduced into changes in cell metabolism as a result of associated changes in cytoskeletal organization and nuclear structure.